# Liver Disease Associated With Exposure to 1,1,1-Trichloroethane

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• **1,1,1-Trichloroethane is a halogenated hydrocarbon solvent commonly used in industry because of its supposed lack of hepatotoxicity. Nonetheless, animal studies performed by several independent groups have shown the solvent to induce fat deposition, vacuolar degeneration, and centrilobular necrosis, changes similar to those seen after exposure to carbon tetrachloride, albeit of a much reduced magnitude, in animals exposed to the agent. Four patients with fatty liver disease whose work entailed substantial exposure to this agent were seen at the University of Pittsburgh (Pa). Based on this clinical experience, we believe that 1,1,1-trichloroethane should be reconsidered as an agent with potential hepatotoxicity in man.**

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Death from cirrhosis and liver disease ranks 10th among the leading causes of death in the United States and 9th among the leading causes of lost years of life before the age of 65 years.[1,2] Although fatty liver disease (FLD) need not necessarily progress to cirrhosis, it is a well-known antecedent of this condition.

The prevalence of FLD has been reported in several autopsy series of accidental deaths. Kuller et al[3] described FLD as being present in 111 of 428, or 25%, of sudden, nontraumatic deaths occurring between the ages of 25 and 64 years in Baltimore, Md. In that series, the proportion of cases of FLD attributable to alcohol was unknown. It is of some interest that Ground,[4] after excluding alcohol-related fatalities, reported FLD as being present in 21% of individuals between the ages of 18 and 58 years who died in road or aircraft accidents in Great Britain in 1984. Similarly, Alcastra[5] reported FLD in 32% of 1534 autopsies performed in Spain, of which less than half could be attributed to alcohol. Moreover, Hartz and Kornhuber[6] reported FLD in 84% of men and 72% of women who died in accidents in Germany; rates one third as high were recorded in nonaccidental deaths. Fatty liver disease has been described in 60% to 90% of morbidly obese individuals and in an uncertain proportion of diabetics.[7-10] Nine percent of persons undergoing jejunoileal bypass for therapy of obesity who have FLD go on to develop cirrhosis.[11] Similarly, FLD associated with diabetes mellitus or obesity is known to progress to cirrhosis.[10] Despite this sequence of events, many primary care physicians ignore the minor elevations in liver injury parameters frequently seen in patients, particularly in those with fatty livers as defined by computed tomographic scanning techniques. This lack of interest exists despite the fact FLD may be an early indicator of progressive liver disease.

Clearly, most cases of FLD are attributed to alcohol abuse. However, only rarely are searches for additional environmental or occupational exposures even undertaken when physicians are faced with a nonalcoholic with a fatty liver. This is the case despite the fact that styrene,[12,13] other aromatic compounds,[14-17] and trichloroethylene (inhaled during glue sniffing)[18,19] have been implicated as important agents in the pathogenesis of liver disease in humans, and these agents are thought to be rare contributors to the problem of cirrhosis on a population basis.

On the other hand, 1,1,1-trichloroethane (1,1,1-TCE) is not considered to have great hepatotoxic potential primarily on the basis of several short-term human laboratory exposure studies,[20-23] one cross-sectional human study in the workplace,[24] and several animal studies.[25-28] As a result of its perceived low hepatotoxic potential, it is widely used in industry. Nevertheless, Klaassen and Plaa[25] have described hepatotoxicity after 1,1,1-TCE and trichloroethylene exposure in dogs, which pathologically appeared to range in severity somewhere between that of tetrachloroethylene and dichloromethane. In rats, hepatotoxicity of 1,1,1-TCE has been seen at 200 times the dose required to produce hepatotoxicity with carbon tetrachloride.[26] McNutt et al[29] described acute inflammation, centrilobar swelling of hepatocytes, vacuolar degeneration and necrosis, and an increase in triglyceride deposits after 1,1,1-TCE exposure. These changes closely resembled those induced by carbon tetrachloride. Finally, Thiele et al[30] have reported a case of FLD that, although originally induced by trichloroethylene exposure, appeared to have its progression and improvement clearly related to an associated 1,1,1-TCE exposure.

Zimmerman[31] has reviewed the factors associated with increasing hepatotoxicity resulting from halogenated hydrocarbon exposure. He states: "Toxicity appears inversely proportional to the negative charge on the halogen atom, to

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carbon-halogen bond energy, and to chain length and directly proportional to ease of homolytic cleavage, number of halogens in the molecule, and to the atomic number of the halogen." Based on this algorithm and on findings of the available animal studies, 1,1,1-TCE would be expected to have some hepatotoxicity potential.

We report four cases of FLD associated with exposure to 1,1,1-TCE seen at the University of Pittsburgh (Pa) in the last 2 years. Three of the first 10 patients seen in our occupational medicine clinic in a study assessing the risk factors for FLD had very similar jobs entailing substantial exposure to this commonly used industrial solvent. The fourth patient, who required liver transplantation, had had intermittent substantial exposures. Although a case series such as this does not prove a causal association, the frequency of the association was striking and raises the question of a causal association between 1,1,1-TCE and FLD.

## REPORT OF CASES

CASE 1.—A 28-year-old white man was referred for the evaluation of FLD. An occupational history revealed that he began working in a powdered metal plant in 1984 as a "quality control inspector." His job included cleaning parts with 1,1,1-TCE in a cold bath approximately 1 to 2 hours per day. In September 1985, his job station was moved to within 4.6 cm (15 ft) of two hot tanks in which 1,1,1-TCE was used as a degreasing agent. No direct exposure to other hepatotoxins could be identified. The plant management at the patient's place of employment stated that perchloroethylene was used at times on rags to wipe parts clean. Industrial hygiene studies, obtained after diagnosis, showed 8-hour time-weighted average exposures of 1,1,1-TCE elsewhere in the plant (after physical modification of the patient's work site) in the range of approximately one tenth of the permissible exposure level. No estimates were available for his former job. Before working for his current employer, he had worked in a textile mill as a spool changer, as a clerk in a grocery store, and as a molding-press operator in a powdered metal plant, all without known exposure to hepatotoxins.

A history of present illness revealed that in the fall of 1985 the patient noted the gradual onset of anorexia, fevers, chills, and unintentional weight loss, and suffered recurrent, episodic illnesses that were never diagnosed or treated specifically. He was removed from work for 10 days and told to abstain from alcohol because of the clinical diagnosis of hepatitis, with resulting improvement in the assessed liver injury parameters and improvement in his symptoms. When he returned to work, with recurrence of exposure but with continuing abstinence from alcohol, his symptoms recurred and slowly worsened through the fall of 1986, when he was again removed from work.

No pertinent medical, social, or family history of liver disease was obtained. The patient had consumed on average six to eight 360-mL (12-oz) cans of beer per weekend since the age of 18 years. However, he failed to meet criteria for a diagnosis of alcohol abuse or alcoholism according to the *Diagnostic and Statistical Manual of Mental Disorders (Third Edition)* and did not score excessively on the Alcohol Use Inventory,[32] a standardized measure for detecting past as well as current alcohol abuse or addiction.

The patient was shown to have FLD by liver biopsy. His clinical characteristics and laboratory results are listed in Table 1. Of particular interest is that his serum alanine aminotransferase levels were consistently greater than his aspartate aminotransferase levels, a finding quite atypical for alcohol-associated liver disease. He had never been exposed to blood or blood products and had no other risk factors for chronic viral hepatitis. Serological tests for viral hepatitis were negative.

After the patient was no longer exposed to 1,1,1-TCE, his symptoms and liver injury parameters again improved. A subsequent liver biopsy showed markedly less steatosis.

CASE 2.—A 27-year-old white man was referred for the evaluation of toxic hepatitis. An occupational history revealed that in 1980 he had begun working as a process technician for a specialty steel manufacturer, with minimal exposure to all finishing processes. His work primarily involved exposure around a heated 1,1,1-TCE tank used for degreasing finished pieces. He was exposed between 5% and 100% of an 8-hour workday. No separate fume hood was available for the tank. He also had occupational exposures to perchloroethylene and 1,1,1-TCE in cold form, as he used both substances daily to weekly, for periods of generally less than 1 hour, on a wipe rag and in open cans used for brush cleaning. Industrial hygiene samples for 1,1,1-TCE obtained over an 11-year period were reviewed. They ranged from 35 ppm (one tenth of the permissible exposure level of 350 ppm) to 17 718 ppm (50-fold the permissible exposure level).

Approximately 6 months (November 1983) before referral and diagnosis, the patient developed progressive fatigue, and 4 months before referral began to note intermittent but progressive pyrosis. The month before evaluation (March 1984), he put in a considerable amount of overtime and noted that all of his symptoms worsened. A diagnosis of "hepatitis" was made on the basis of elevated serum enzyme levels (Table 1). No prior measures of liver injury were available. An upper gastrointestinal series, barium enema, and a liver-spleen scan were performed and the findings were interpreted as normal.

The patient's medical, family, and social histories were noncontributory. He consumed approximately one six-pack of beer per week. He had never been exposed to blood or blood products and had no other risk factors for chronic viral hepatitis. Serological tests for hepatitis B were negative.

The results of physical examination were normal. Liver injury parameters and the findings of the liver biopsy are shown in Table 1. As in the previous case, the alanine aminotransferase levels were always greater than the aspartate aminotransferase levels, and the level of γ-glutamyltransferase was only minimally increased.

CASE 3.—A 45-year-old white man was referred for evaluation of abnormal results on liver function studies. An occupational history revealed that he had worked as a machinist for 19 years in a tool-and-die section. He cleaned parts by dipping them into cold 1,1,1-TCE. Although he occasionally used several other nonhalogenated hydrocarbons and one halogenated paraffin in his work, each of these agents was considered to possess even less hepatotoxicity than 1,1,1-TCE. He had, on very rare occasions, used perchloroethylene, also on wipe rags.

A review of the patient's medical history revealed that in 1981 an elevation in alanine aminotransferase level (twice normal) was identified. Serological tests performed at that time were negative for hepatitis A and B. In 1983 the patient reported recurrent episodes of abdominal pain and cramping. In 1984 aspartate aminotransferase and γ-glutamyltransferase levels were found to be just above the upper limit of normal. The patient's medical, social, and family histories were noncontributory. The patient credibly denied all alcohol consumption and scored appropriately on the Alcohol Use Inventory.[32] He had never been exposed to blood or blood products and had no other risk factors for chronic viral hepatitis. Serological tests for hepatitis B were negative.

Physical examination revealed a mildly enlarged firm liver with a rounded edge. An upper gastrointestinal series, barium enema, and a liver-spleen scan were performed and the findings were interpreted as normal except for the presence of possible gastric varices. Upper gastrointestinal endoscopy confirmed the finding of esophageal and gastric varices; liver biopsy revealed fatty metamorphosis and inactive cirrhosis.

CASE 4.—A 50-year-old man was referred for evaluation for liver transplantation because of solvent-induced cirrhosis. An occupational history revealed that he had worked for a public utility as a machinist beginning in 1975. In his first 5 years he remembered working with trichloroethylene on approximately five occasions. Beginning in 1980, he worked with cold 1,1,1-TCE one to four 8-hour shifts at a time. He estimated his exposure to that agent at approximately 10% of his working hours. In addition, he was in the vicinity while electricians sprayed 1,1,1-TCE on several occasions (simulations revealed exposures in the range of 350 to 500 ppm). He had worked as a lathe operator in a variety of tool-and-die and machine shops from 1957 to 1975. Only between 1963 and 1965 was there even a remote possibility of solvent exposure, through the presence of a vapor degreaser far away from his job station in his workplace.

He presented with fatigue, nausea, and pain in the right upper quadrant of his abdomen in 1985. Physical examination revealed an obese man whose liver was firm with a rounded edge. Because of liver function abnormalities in a never-in-a-lifetime drinker, a biopsy specimen was obtained and demonstrated cirrhosis. Moreover, the patient had never been exposed to blood or blood products and had no

Table 1.—Clinical Parameters and Liver Biopsy Results*

| | Case No. | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Age, y | 28 | 27 | 45 | 51 |
| Height, cm | 170 | 175 | 163 | 165 |
| Weight, kg | 98 | 90 | 76 | 99 |
| Quetelet index† | 34.2 | 29.4 | 29.2 | 36.7 |
| Laboratory studies | | | | |
| ALT, IU/L (<37) | 96-136 | 24-121 | 97-151 | 38-38 |
| AST, IU/L (<34) | 45-72 | 25-45 | 46-98 | 52-64 |
| γ-GT (<44) | 88 | 34-53 | 41 | 58 |
| Alkaline phosphatase, IU/L (<100) | 79-81 | 85-90 | 30-97 | 115-129 |
| Albumin, g/L (3.5-5.0) | 4.1 | 3.3 | 4.6 | 2.4-3.6 |
| Prothrombin time, s (11-13) | 13.1 (11.8) | 12.4 (11.8) | ... | 14.1 (11.8) |
| Liver size (by CT scan), $cm^3$ (1200-1500) | 2761 | 1779 | ... | 1289 |
| Liver biopsy | | | | |
| Histologic findings | Macrovesicular | Macrovesicular | Macrovesicular | Macronodular cirrhosis with dysplastic nuclei and piecemeal necrosis |
| Degree of fat | 4+ | 1+ | 3+ | 3+ |
| Zone | III | Mixed | I<III | III |
| Perivenular fibrosis | + | − | − | − |
| Sinusoidal fibrosis | + | − | − | − |
| Periportal fibrosis | + | + | + | + |
| Cellular infiltrate | Polynuclear cells | Mononuclear and polynuclear cells, eosinophils | Mononuclear cells | Mononuclear cells |
| Architecture | Intact | Intact | Intact | Intact |

*ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyltransferase; CT, computed tomographic; plus sign, present; and minus sign, absent.

†Weight in kilograms divided by height in meters squared.

other risk factors for chronic viral hepatitis. Serological tests for hepatitis B were negative.

## COMMENT

All four patients presented with FLD without other predisposing causes, although two can be classified as obese (Quetelet index greater than 30). Alcohol consumption was not in the range associated with steatosis (maximum, 66 mL [2.2 oz] per day). The one patient whose pattern of liver injury parameters was consistent with alcohol injury had never consumed alcohol. None of the patients had received blood or blood products, was diabetic, had sexual habits associated with viral hepatitis, or demonstrated serological evidence of prior hepatitis B or other viral infection. The primary exposure in all four was 1,1,1-TCE, although minimal exposures to other known hepatotoxins (perchloroethylene and ethanol) could be documented in three and two of the four cases, respectively.

Nonalcoholic FLD is a well-recognized though poorly studied syndrome.[11] Known risk factors include obesity, diabetes, and intestinal bypass surgery. Although between 40% and 85% of morbidly obese patients presenting for therapeutic intervention have FLD on biopsy, only 2.7% of morbidly obese individuals in a working population had evidence of abnormal results on liver tests.[33] Hepatotoxin exposure is generally considered a rare cause, although, to our knowledge, no reports of nonalcoholic FLD have systematically investigated the presence of liver toxins.[34,35] Although 1,1,1-TCE is reportedly a very frequently used solvent, we have seen no patients with such exposures with other forms of liver disease among hospitalized patients at our institution and were therefore struck by the frequency of the association.

The industrial and environmental use of 1,1,1-TCE as a solvent has increased substantially during the last several decades, because of its assumed lack of hepatotoxicity. This assumption, however, is based on the findings of a single cross-sectional study and several laboratory exposure studies performed on a few humans and ignores a body of data obtained in animal studies that suggest that 1,1,1-TCE may be hepatotoxic.

Because the usual criteria for liver toxicity, such as alterations in the results of liver injury tests, are not readily translated into dose-response curves, Plaa et al[26] evaluated the toxicity of seven halogenated hydrocarbons in mice by measuring sleeping time, sulfobromophthalein retention time, and morphological characteristics of the liver. In these studies, 1,1,1-TCE demonstrated the least toxicity of the several agents investigated but nonetheless showed hepatotoxic potential.

In a later study, Klaassen and Plaa[25] compared the hepatotoxicity of seven different compounds by constructing dose-response curves for aspartate aminotransferase and liver histology. They divided the hydrocarbons they studied into two groups, those causing centrilobular necrosis at near-lethal doses (carbon tetrachloride, chloroform, and 1,1,2-

TCE) and those that did not (1,1,1-TCE, dichloromethane, trichloroethylene, and tetrachloroethylene). At 50% of the dose necessary to cause measurable organ dysfunction, only 1,1,1-TCE failed to cause vacuolization of centrilobular hepatocytes. The duration of induced alanine aminotransferase abnormalities, on the other hand, was similar for the five hydrocarbons other than chloroform and carbon tetrachloride.

Prendergast et al[27] examined rats, guinea pigs, and several other types of animals under long-term (90 days) continuous and intermittent (5 days per week, 8 hours per day) exposure to 1,1,1-TCE. No evidence of liver injury was seen after continuous exposure at 370 or 135 ppm, although at the latter dose a surprising number of animals died.

McNutt et al[29] exposed mice over varying periods of time to 1,1,1-TCE and found changes closely resembling those induced by carbon tetrachloride. They described acute inflammation, centrilobar swelling of hepatocytes, vacuolar degeneration and necrosis, and an increase in triglyceride deposits, all changes consistent with and suggestive of FLD.

Further supporting studies, published earlier, were summarized by Aviado et al.[36] These authors reviewed the hepatotoxicity of 1,1,1-TCE in dogs, rabbits, guinea pigs, rats, and mice, as known before 1976.

A series of studies performed at the Dow Chemical Toxicology Research Laboratories, Midland, Mich,[20,22] demonstrated that a concentration of 500 ppm of 1,1,1-TCE was safe for animals, even after long-term exposures. These studies and two others[21,23] also examined the effects of 1,1,1-TCE vapors on humans. The results are summarized in Table 2. Only after the induction of anesthesia were minimal functional abnormalities of the liver demonstrated. On the other hand, the longest duration of exposure was only 5 days, and no long-term follow-up was performed.

Finally, one cross-sectional study has been published comparing workers exposed to 1,1,1-TCE with an unexposed population.[24] Exposures over a 2-year period ranged from 100 to 350 ppm. Mean alanine aminotransferase levels were actually significantly lower in the exposed workers than in the unexposed workers. Recently, such phenomena in cross-sectional studies have been interpreted as evidence for a "survivor effect." If ill individuals leave the work force preferentially, the remaining members are "healthier," showing fewer laboratory abnormalities and better survival characteristics. Interestingly, a greater proportion of exposed than unexposed workers (28 vs 21) experienced "abnormalities of the gastrointestinal system" by history, although the significance of this finding is uncertain. The excess symptom rate could be interpreted as an early indication of liver disease not yet associated with abnormal results of liver tests. When disease then becomes severe enough to produce measurable abnormalities, individuals would leave the work force.

Thiele et al[30] described a patient with liver disease that was initially thought to have been caused by exposure to trichloroethylene. After removal from exposure and subsequent improvement, exposure to 1,1,1-TCE was associated with progressive deterioration of liver function. Cessation of exposure was again temporally related to improvement. Several earlier reports concerning acute toxicity in humans[37-39] have also been published.

Two independent mechanisms are considered to contribute to the hepatotoxicity of halogenated hydrocarbons. First, the blockage of nascent lipoprotein coupling with triglyceride leads to accumulation of triglyceride within cells. This accumulation of fat can lead to progressive liver injury.[40] However, the exact cause or mechanism responsible for fat-induced hepatic necrosis is unclear. The second hypothesis is that FLD may be related, at least in part, to the production of toxic-free radicals and/or peroxidation injury.[41-45] In general, metabolites formed in phase 1 reactions (mixed-function oxidase reactions) are more toxic than are their parent compounds.[46] Thus, even xylene and other nonhalogenated hydrocarbons, currently considered nontoxic, can give rise to toxic intermediaries as a consequence of mixed-function oxidase metabolism prior to their excretion. Alcohol, which is thought to lead to hepatic damage, at least in part, as a result of free radical formation,[47-49] has been shown to potentiate the toxic effects of organic solvents and drugs that can exert at least some of their toxicity through lipid peroxidation.[31,50-56] Recent evidence indicates that short-chain aliphatic hydrocarbons without intrinsic hepatotoxicity may potentiate halogenated hydrocarbon exposures; eg, acetone increases both the acute

Table 2.—Summary of Human Exposure Chamber Studies of 1,1,1-Trichloroethane*

| Source, y | No. of Subjects | Exposure Concentration, ppm | Duration, min | Frequency (No. of Times Exposed) | Health Effects/ Liver Injury |
|---|---|---|---|---|---|
| Torkelson et al,[20] 1958 | ?1 | 546 | 90 | 1 | NM |
| | ?1 | 506 | 450 | 1 | NM |
| | ?1 | 1000 | 30 | 1 | NM |
| | ?1 | 920 | 70-75 | 1 | NM |
| | ?1 | 1900 | 5 | 1 | NM |
| Stewart et al,[21] 1961 | 6 | 500 | 78 | 1 | Normal |
| | 6 | 500 | 186 | 1 | Normal |
| | 3 | 1000 | 73 | 1 | Normal |
| | 2 | 1000 | 35 | 1 | Normal |
| | 3 | 1000 | 20 | 1 | Normal |
| | 7 | To anesthesia (<2650) | 15 | 1 | Normal† |
| Rowe et al,[22] 1963 | NM | 520 | 420 | 1, 4, 5 | None |
| Stewart et al,[23] 1969 | 2-5 (a total of 11 volunteers in 31 exposures) | 500 | 6.5-7 | 5 | AST, LDH unchanged |

*NM indicates not mentioned; AST, aspartate aminotransferase; and LDH, lactate dehydrogenase.
†Two of the seven subjects developed transient elevation of uroporphyrin excretion.

and chronic hepatotoxicity of carbon tetrachloride in animals.[57]

The histologic characteristics of FLD are well described. Currently, most investigators classify it by its zonal distribution within the liver and according to the size of the fat droplets within hepatocytes.[31] Although a considerable amount of literature has been accumulated on drug-induced hepatitis, little information is available on the importance of occupational and environmental risk factors for liver disease in general and for steatosis specifically. In one recent study of blood donors with elevated alanine aminotransferase levels,[58] 22% were obese and 63% consumed alcohol "daily." No mention was made of occupational or environmental exposures to liver toxins. Moreover, the role of steatosis as a cause for or predecessor of cirrhosis in nonalcoholics who are neither obese nor diabetic and who show no evidence of viral disease has not been assessed. Exceptions are the recent epidemics resulting from exposures to kepone,[59] trichloroethylene,[18] and dimethylformamide.[60] However, only chloroform- and carbon tetrachloride–induced liver disease (both steatosis and cirrhosis) have been well described and are generally accepted to be causes of both acute hepatotoxicity and chronic liver disease.

Two of our four patients were clearly obese, ie, 30% overweight. The other two were not thin. Two mechanisms might play a role involving the interaction of obesity and hydrocarbon exposure in the development of liver disease. First, it is known that the potentiation of hydrocarbon toxicity by alcohol is dependent in part on the relative timing of alcohol administration.[61] The presence of obesity may continuously present the liver with more substrate to form more epoxides. The continuous low-level presence of free radicals may then allow additional exposure to the more potent halogenated hydrocarbons and thereby induce overt damage more readily. Second, fatty tissue may itself serve as a reservoir of halogenated hydrocarbons. These would then be continuously released over a much longer period of time than in individuals with less body fat, leading to an effectively much longer duration of exposure. A final additional contribution to toxicity in these cases may result from minimal exposures through contamination of commercially available 1,1,1-TCE or ground water with minimal amounts of solvents with substantially greater hepatotoxicity, such as trichloroethylene and perchloroethylene. Although we cannot absolutely discount such "part per million" contamination, we think it unlikely to play a major role.

In animal experiments, alcohol potentiates the effects of other hepatotoxins. Three of the four patients consumed minor quantities of alcohol, of a magnitude not generally associated with the development of FLD. We obviously cannot exclude an interaction between the toxicities of alcohol and 1,1,1-TCE. Both obesity and alcohol may therefore have played a role in the pathogenesis of liver disease in these cases.

In summary, 1,1,1-TCE has been assumed to be free of hepatotoxicity in humans because the scanty evidence available has failed to demonstrate clear evidence of hepatotoxicity rather than because it has been studied extensively—a type II error, or lack of power in documenting safety, rather than the certainty of safety. In addition to epidemiological evidence, animal bioassays and structure-activity relationships are commonly used by toxicologists in interpreting possible causal associations.[62] Although many physicians hesitate to use animal studies to support causal associations in humans, in this case human hepatotoxicity might reasonably be expected, based on the evidence from animal studies. Human studies have not demonstrated lack of effects. Case series such as this cannot conclusively document the hazardous nature of an agent. Still, we are left with an agent (1) that has been shown to induce liver disease in animals, (2) that is associated with some degree of liver dysfunction in humans after substantial exposure, and (3) that has not been shown to be safe. On the basis of these four cases, we believe that 1,1,1-TCE may be a potential hepatotoxin in humans.

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